

## REMARKS

In response to the Final Rejection, a Request for Continued Examination (RCE) is being submitted herewith along with a Declaration signed by Dr. Jean E. F. Rivier, which responds to the points made in the section 112 rejection that it was uncertain that the inventors would have had the invention as claimed in their possession at the time of the filing of the application. In this respect, new claim 15 is submitted herewith, which contains fewer and more limited substitutions than original claim 1; it is generally patterned after dependent claim 2. Claims 1, 2 and 9 are cancelled, and claims 5, 6, 7 and 12 are amended so as to depend from new claim 15. Claim 11, which was indicated as being free from prior art (along with claims 3 and 12), has been amended to make it an independent claim. Claims 3 and 12 are amended to depend from claim 13. Claim 12 is also amended to correct a clerical error in line 3; it was intended that the peptide recited as the first of the three molecules in this claim should be the compound that was synthesized in Example 5 on page 21 of the specification.

Claim 13 has been amended so that all of its recitations include only residues that appear in a CRF analog set forth in one or more of Examples 1, 4, 5, 5A, 5B, 5C, 5D, 5E, 6A, 6B, 6C, 6D, 6E, 6F, 6G, 6H and 6I, except for the acyl group at the C-terminus, for which the accompanying declaration of Dr. Jean Rivier is pertinent. Claim 14 has been similarly amended so that the only variable, i.e. the group Y<sub>1</sub> at the N-terminus of the peptide, is now defined consistent with the declaration of Dr. Rivier.

Review of the Dr. Rivier's declaration will show that, as a result of the 25+ years of synthesizing CRF analogs, he is comfortably able to state his opinion that, with respect to a good number of the positions in the 41-residue amino acid sequence of human CRF, certain conservative changes may be made which would have no significant effect on the binding affinity of the analog to the CRF receptors. New claim 15 is drafted consistent with the statements that appear in Dr. Rivier's declaration. In the penultimate paragraph of his declaration, Dr. Rivier points out that many of these CRF analogs have been made which have incorporated multiple of these conservative substitutions, and it was found that no cumulative significant effect on the binding of the ligand to CRF receptors

resulted from the inclusion of multiple of these conservative substitutions in the AA sequence of the native peptide regardless of the number of them that were made. It is submitted that Dr. Rivier's declaration stands as clear evidence that, at the time of filing of the application, the inventors possessed the subject matter of present claim 15. This claim now recites the four key criteria that result in the differential selective binding (in the context of the overall amino acid sequence of CRF) as defined in paragraph 5 of Dr. Rivier's declaration; the remaining residues are now defined as only single amino acid residues or as conservative amino acid substitutions.

While admitting that the level of skill in this art of peptide synthesis is high, the Examiner would argue that there is no disclosure of a correlation between the function and structure of the compounds. This is not the case. The important chemical structural characteristics of the molecule are set forth in Dr. Rivier's declaration in paragraph 5 and also in the specification, where it is pointed out that it is these particular chemical structural features that give rise to the important biological functional characteristics; i.e. high binding affinity for CRFR1 and only weak binding affinity for CRFR2.

Except for claim 14 (which finds support in Example 1 at page 17, line 33 to page 18, line 7), Applicants are not claiming specific agonist properties of the resultant peptides. The claim language is clear that differential binding is an important trait, and such differential binding to CRFR1 (in contrast to CRFR2) is specified as the unique characteristic of the peptides defined by the rest of the claims.

The mere fact that the permutation of compounds that could result from potential multiple substitutions at different locations in the amino acid sequence as defined in new claim 15 may be a reasonably large number should not be a determining factor. Because each of the individual substitutions has been shown not to have any significant effect on the binding of the 38- or 39-residue long CRF analog, either individually or cumulatively, the size of the ultimate number of permutations should be not be of particular concern. As Dr. Rivier clearly states, these particular conservative substitutions have over the past 25+ years been shown to be fully compatible with the

biological functions of the CRF molecule and not to significantly affect its binding to receptors. Accordingly, it is submitted that claim 15 should be allowable.

Independent claim 13 and dependent claims 5, 6, and 7 contain far fewer potential substituents to the native sequence of human CRF than does claim 15, and they would thus encompass far fewer compounds. Likewise, all of these conservative substitutions in claim 13 are among those to which Dr. Rivier makes reference in the accompanying declaration. More specifically, claim 7 recites only 6 positions with conservative substitutions in addition to the N-terminus, and analogs including each one of these substitutions are set forth in Examples 1, 2, 4, 5C, 6E and 6G.

As set forth in the second paragraph of these Remarks, amended claim 13 contains only conservative potential substitutions found within one of the specified examples, and claims 3 and 12 depend therefrom. Accordingly, it is submitted that these claims 13, 3, 5, 6, 7, 11 and 12, which would encompass fewer permutations, should be allowed. It was earlier indicated that claims 3, 11 and 12 were considered to be free of prior art.

Independent claim 14 is directed to the cyclic and linear compounds that were synthesized and tested as described in Example 1 of this application. The acyl group at the N-terminus of the analogs synthesized and tested was acetyl. U.S. Patent No. 4, 415, 558 issued to the Salk Institute for Biological Studies, based upon an application filed in May 1982, more than 25 years ago; in this 1982 application, it was pointed out that, at the N-terminus, there could be an acyl group having 7 or less carbon atoms or hydrogen. It is submitted that this claim, reciting only this single substitution (which is also discussed in Dr. Rivier's declaration), may not fairly be rejected based upon section 112, first paragraph, and it is submitted that claim 14 should be allowed.

In view of the foregoing amendments and Dr. Rivier's declaration, and in the absence of any pertinent prior art, it is submitted that claims 3, 5-7, and 11-15 should be allowed, and allowance thereof is respectfully requested. A Notice of Allowance is courteously solicited.

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Respectfully submitted,

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